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Turkish Journal of Endocrinology and Metabolism, (2003) 4 : 169-174 **ORIGINAL ARTICLE**

Relationship of Early Atherosclerotic Vascular Changes with Serum Lipoprotein(a) in Predialysis Chronic Renal Failure and Maintenance Hemodialysis Patients

Hamid Nasri* **Azar Baradaran****

** Shahrekord University of Medical Sciences, Hajar Medical, Educational and Therapeutic Center, Section of Hemodialysis, Shahrekord, Iran*
*** Department of Biochemistry, The Center of Research and Reference Laboratory of Iran.Hospital Bou-Ali, Damavand st. Tehran. Iran*

In renal failure studies revealed an increase in plasma concentration of lipoprotein(a)[Lp(a)]. Elevated plasma Lp(a) levels in chronic renal failure patients is recognized as an independent risk factor for premature atherosclerotic coronary heart disease. In this study we aimed to consider the effect of serum plasma Lp(a) levels on early structural atherosclerotic vascular changes in a group of CRF patients not yet on dialysis and end-stage renal disease patients under regular hemodialysis.This study is cross-sectional which was done on chronic renal failure (CRF) patients not being on hemodialysis yet and hemodialysis patients who were underwent regular hemodialysis because of end-stage renal failure. For patients serum Lp(a) was measured. Carotid intima-media thickness (carotid-IMT) was measured and carotid-femoral artery for plaque occurrence (plaque score) by B-mode ultrasonography was determined. Twenty-nine normal subjects (group one) (F=17 M=12), thirty-three chronic renal failure patients not yet on hemodialysis (group two)(F=19 M=14) and forty-three (F=19 M =24) hemodialysis patients due end-stage renal disease (group three) were considered. Mean±SD of LP(a) in group one were 42.0±20.0 mg/dl. The serum LP(a) of CRF group was 57.0±23.0 mg/dl and for HD group was 55.0±16.0 mg/dl. The IMT of group one was 0.84±0.20 mm.Mean±SD of IMT of CRF group and HD group were1.30±0.40 mm and 1.10±0.30 mm respectively. Ninety-three percent of persons of group one had zero plaque score while 39.4% of patients of group two and 51.2 %of patients in group three had zero plaque score more over 6.8% of subjects in group one, 24.3% in group two and 25.6% of patients in group three had plaque scores between 1&2. Also for plaque scores of 3&4, group one had zero plaque score, group two had 36.4% and group three had 23.3% plaques in scores of 3&4. Significant difference of IMT of group one with group two ($p<0.001$)and with group three ($p=0.008$) were seen. Significant difference of carotid- IMT of group two with group three ($p=0.023$) was found too. Significant difference of LP(a) of group one with group two ($p=0.016$) was seen and significant difference of LP(a) of group one with group three ($p=0.021$) was demonstrated too. No significant difference of LP(a) of group two with group three ($p>0.05$) were found. Significant differences of plaque score between group one with group two ($p<0.001$) was seen also significant difference of plaque score between group one with group three ($p=0.020$) was found. No significant difference of plaque score of group two with group three ($p>0.05$) was found. Significant positive correlation of serum LP(a) with carotid- IMT and also significant positive correlation of serum LP(a) with plaque score in hemodialysis patients were found. The present study showed positive relationship of serum LP(a) with carotid- IMT and arterial plaques in hemodialysis patients. Lipoprotein(a) as a non traditional factor in progression of atherosclerosis have an important role in acceleration of atherosclerosis and cardiovascular diseases observed frequently in hemodialysis patients and needs more attention.

Key words: Intima-media Thickness, Lipoprotein(a), Hemodialysis, Chronic renal failure, Plaque score

Correspondence address:
Hamid Nasri M.D
Internist, Nephrologist, Assistant professor of Shahrekord University of Medical sciences.Hajar Medical, Educational and Therapeutic Center, Section of hemodialysis – Shahrekord, Iran.
Tel : 0098 911 2439584
E-mail : hamidnasri@yahoo.com
Tel : 0098 381 2220016(Hospital) Tel : 0098 381 2223350
Fax : 0098 381 2243715 (hospital)

Introduction

Lipoprotein(a) [Lp(a)] when present in high levels in plasma is recognized as an independent risk factor for premature atherosclerotic coronary heart disease (1). In renal failure studies revealed an increase in plasma concentration of Lp(a) (1-3). Elevated plasma Lp(a) levels in chronic renal failure patients have been

associated with a frequency distribution of apolipoprotein(a) [apo(a)] isoforms Similar to those found in general population. This indicates that elevated Lp(a) levels in these patients are not due to genetic origin (4-6). Therefore it has been suggested that kidneys have an important role in Lp(a) metabolism, decrease Lp(a) catabolism or increase of liver production (7-10). Increased Lp(a) levels could be a contributing factor in the increased incidence of atherosclerotic disease observed in CRF and hemodialysis patients (11-12). The early stages of artherosclerosis are associated with changes in arterial structure. Subtle structural changes such as thickening of arterial intimae-media complex thickness (IMT) occur early in the atherosclerotic disease process (12-14). Using B-mode ultrasonography for assessing early athero-sclerosis is safe and non-invasive to study superficial vascular districts, such as the carotid or femoral artery (11-13). Therefore ultrasonic evaluation of carotid artery for IMT can identify patients at risk for cardiovascular disease (12-14). Indeed carotid arteries are privileged area for studying the progression of atherosclerotic lesions from onset to fully developed plaque. Carotid- IMT measurements are strongly related to the extent of atherosclerosis in other vascular districts too (11-14). As many known and conventional risk factors have been shown to be significantly associated with increased arterial wall thickness, consistent with their accepted role in atherogenesis, much less is known however about the effects of Lp(a) on IMT of CRFand hemodialysis (HD) patients (15). Therefore in this study we firstly aimed to consider the effect of plasma Lp(a) levels on early structural atherosclerotic vascular changes in a group of CRF patients not yet on dialysis and end-stage renal disease patients under hemodialysis and secondly we aimed to consider the correlation of Carotid artery-IMT and carotid-femoral artery plaques with other lipids mentioned in the study and duration of disease.

Patients and Methods

This is a cross-sectional study that was carried out on patients with chronic renal failure not yet on dialysis and end-stage renal disease patients undergoing maintenance hemodialysis treatment. For patient selection exclusion criteria were cigarette smoking, body mass index more than 25, anti lipid drug taking, recent MI and vascular diseases and also active or chronic infection and diabetes mellitus were the other exclusion criteria. Group one were healthy persons who had no history of hypertension or renal disease. Group two were chronic renal failure(CRF) patients not being on hemodialysis yet and group three were hemodialysis patients who were underwent regular hemodialysis because of end-stage renal failure. For laboratory exams, after 14 hour overnight fasting blood sampling were done. For group one and two blood sampling were done from antecubital vein for group three blood samples were obtained from venous line of hemodialysis apparatus at the beginning of hemodialysis. Fasting blood suger (FBS), lipoprotein (a) [Lp (a)], Triglyceride (TG), Cholestrol (Chol), HDL-C, LDL-C, Bun, Creatinin were measured. Lp(a) was measured by enzyme immunoassay (ELISA) by Immuno-biological laboratories (IBL) kit of Hamburg. Oher lipids mentioned above and BUN, Creatinin and FBS were measured by standard kits. Serum LDL-C was calculated by friedewald's formula (16). Creatinine clearance was evaluated from serum creatinine, age and body weigh (17). Subjects in group one were interviewed using a questionnaire prior to consent ascertain that were free from any clinical evidence or history of diabetes, cardiac or vascular disease and had no past or current history of hypertension or any renal disease. The clinical history of patients in groups two and three was determined by medical records of hospital. Carotid and femoral artery sonography were done by a single sonologist unaware of history or lab data of patients. Using a Honda-Hs-2000 Sonograph with 7.5 MHZ linear probe IMT in mm was measured and carotid-femoral arterial plaque (plaque score) were determined. The procedure was done at the end of diastolic phase. The sites of measurements were at the distal common carotid artery, area of bifurcation and at the first proximal internal carotid artery. Carotid-IMT was measured at the plaque free areas. For examination. Subjects were in supine position with neck hyperextension and rotation of head for facilitation of procedure performing. By sonography, the carotid artery found to has tree different echoes. Intimae- media thickness (IMT) was defined as the distance from leading edge of lumen-Intimae interface of the far wall to the leading edge of the media- adventitia interface of the far wall. Caritid-IMT more than 0.8 mm was considered abnormal. For statistical analysis we considered the mean of right and left

carotid artery- IMT. Sonography for plaque was done at the right and left of carotid and femoral arteries and scored from 0 (no plaque) to score 4 (plaque presence at all four sites) regardless of the number and size of the plaques in each site plaque occurrence in each site scored one point plaques was considered as a local intimal thickness more than 1 mm. For plaque measurement the largest longitude was considered. For statistical analysis descriptive data are expressed as Mean±SD and frequency distributions. For comparison between groups ANOVA, Scheffe and Chi-Square tests were used. For correlations partial correlation test with adjustment for age and regression analysis with stepwise method were used and all statistical analysis were performed using SPSS (version 11.00). Probability (p) was considered significant when $p< 0.05$.

Results

The total subjects were 105 (F=55 M=50) consisting of 29 normal, healthy subjects (control group= group one) (F=17 M=12) 33 chronic renal failure patients not yet on hemodialysis (CRF group= group two) (F=19 M=14) and 43 hemodialysis patients due end-stage renal disease (HD group= group three) (F=19 M =24). Table 1 show the characteristics of subjects. Table 2 show the mean±SD of laboratory data of subjects. Table 3 show the frequency distribution of plaque score in subjects. Mean±SD of known duration disease in CRF patients were36±20 months. Mean±SD of the length of the time patients have been on hemodialysis were 44±31 months. Group one had normal creatinin clearance, Mean±SD of creatinin clearance of group two were 31±18 and for HD group the creatinin clearance of below 10 cc/min was envisaged. The serum LP(a) in group one and CRF group and also in HD group were 42.0±20.0 and 57.0±23.0 mg/dl and 55.0±16.0 mg/dl respectively. Mean±SD of carotid- IMT in group one was 0.84±0.20 mm. The carotid- IMT of CRF and HD group were 1.30±0.40 mm and 1.10±0.30 mm respectively. Ninety-three percent of subjects of group one had zero plaque score while 39.4% of patients of group two and 51.2 %of patients in group three had zero plaque score and also 6.8% of subjects in group one, 24.3% of patients in group two and 25.6% of patients in group three had plaque scores between 1&2. More over for plaque scores of 3&4 group one had zero plaque score group two had 36.4% and group three had 23.3% plaques in scores of 3&4. All of the plaques were calcified. By ANOVA there were significant difference of carotid- IMT ($p<0.001$), LDL-C ($p<0.001$), Cholestrole ($p<0.001$), and LP(a) ($p=0.006$) between three groups. No significant difference of Triglycerid (TG) and HDL-C between three groups were found ($p>0.05$). Significant difference of carotid- IMT of group one with group two ($p<0.001$) was seen and significant difference of carotid- IMT of group one with group three ($p=0.008$) was demonstrated too. More over significant difference of carotid- IMT of group two with group three ($p=0.023$) was found (Scheffe test). Significant difference of serum LP(a) of group one with group two ($p=0.016$) was found and significant difference of serum LP(a) of group one with group three ($p=0.021$) was seen too and no significant difference of carotid- IMT of group two with group three ($p=0.962$) was found (Scheffe test). Significant differences of plaque score between three groups ($p= 0.02$) (Chi-Square test) were seen. Scheffe test showed significant difference of group one with group two ($p<0.001$) and also significant difference of group one with group three ($p=0.020$) was demonstrated and no significant difference of plaque score of group two with group three ($p>0.05$) was found. Ninety-eight percent of patients in groups two and three were hypertensive that were taking antihypertensive therapy and were near control.Mean ±SD of systolic blood pressure in group two and three were 130 ± 20 mmHg. Mean± SD of diastolic blood pressure in group two and three were 80±20 mmHg there was not significant difference between hypertention of group two with three ($p>0.05$). There was a significant positive correlation between IMT and age in group one ($p=0.035$), group two ($p=0.017$) and group three ($p=0.019$) (regression analysis with stepwise method). In normal persons significant positive correlation of carotid- IMT with LDL-C ($r =0.350$ $p= 0.03$) was seen and significant linear inverse correlation of carotid-IMT with HDL-C ($r = -0.405$ $p= 0.02$) was found too and also marginal correlation of carotid-IMT with TG ($r =0.310$ $p= 0.05$) were found. No significant positive correlation of carotid-IMT with serum LP(a) ($r =0.240$ $p> 0.05$) was demonstrated and no significant positive correlation of carotid-IMT with serum Chol (r =

0.260 p>0.05) were found too, more over no positive correlation of carotid-IMT with plaque score (r =0.101 p>0.05) was found in this group also no positive correlation of plaque score with serum LP(a) , LDL-C, HDL-C, Chol and TG were found too (p>0.05) (Partial correlation test after adjustment for age). In CRF group significant positive correlation of carotid-IMT with plaque score (r =0.500 p= 0.002) was seen. No positive correlation of carotid-IMT and also plaque score with serum LP(a), LDL-C, HDL-C, Chol and TG were found (p>0.05) (partial correlation test after adjustment for age, Clearance of Creatinin and known duration of disease) in CRF group. In this group significant linear inverse correlation of creatinin clearance with serum LP(a) (r = -0.441 p= 0.040) (Figure 1) was seen. No significant positive correlation of carotid-IMT and also plaque score with Creatinin Clearance (p>0.05) were found (partial correlation test after adjustment for age) in CRF group. In HD group, significant positive correlation of carotid-IMT with serum LP(a) (r =0.298 p= 0.029) (Figure 2) was found. Significant positive correlation of plaque score with serum LP(a) (r =0.375 p= 0.008) (Figure 3) was found too in hemodialysis patients. No significant positive correlation of carotid-IMT and also plaque score with Chol , LDL-C, HDL-C, and TG were found in HD patients (p>0.05), more over no significant positive correlation of carotid- IMT with plaque score (r =0.222 p>0.05) was found (partial correlation test after adjustment for age) in this group.

Table 1. Frequency distribution of Ag (year), D.D: duration of disease (months) and Clearance of Creatinin (CLcr) (cc/min).

Variables		mean±SD	Minimum	Maximum
Group 1	Age	45 ±10.4	20	70
	D.D	-	-	-
	CLcr	103±4	98	110
	IMT	0.84±0.20	0.50	1.20
Group 2	Age	62±14.5	30	88
	D.D	36±20	2	76
	CLcr	31±18	10	70
	IMT	1.30±0.40	0.60	2.0
Group 3	Age	47±16.4	15	78
	D.D	44 ±31	6	108
	CLcr	<10	<10	<10
	IMT	1.10±0.30	0.50	1.70

D.D in group two: Known duration of CRF.
D.D in group three: The length of the time patients had been on hemo-dialysis.

Table 2. Frequency distribution of lipids (mg /dl).

Variables		Mean±SD	Minimum	Maximum
Group 1	Lp (a)	42.0±20.0	10	94
	Chol	203±41	125	340
	LDL-c	126±34	75	230
	HDL-c	41±10	25	65
	Tg	154±73	50	325
Group 2	Lp (a)	57.0±23.0	15	135
	Chol	211±70	100	390
	LDL-c	136±52	45	300
	HDL-c	33±13	15	85
	Tg	171±100	60	550
Group 3	Lp (a)	55.0±16.0	25	95
	Chol	148±35	95	930
	LDL-c	97±28	40	160
	HDL-c	33±18	20	90
	Tg	145±62	40	230

Table3. Frequency distribution of plaque score in groups.

	plaque score	Frequency	Percent
Group 1	0	27	93
	1	1	3.4
	2	1	3.4
	3	0	0
	4	0	0
Group 2	0	13	39.4
	1	5	15.2
	2	3	9.1
	3	3	9.1
	4	9	27.3
Group 3	0	22	51.2
	1	3	7
	2	8	18.6
	3	2	4.7
	4	8	18.6

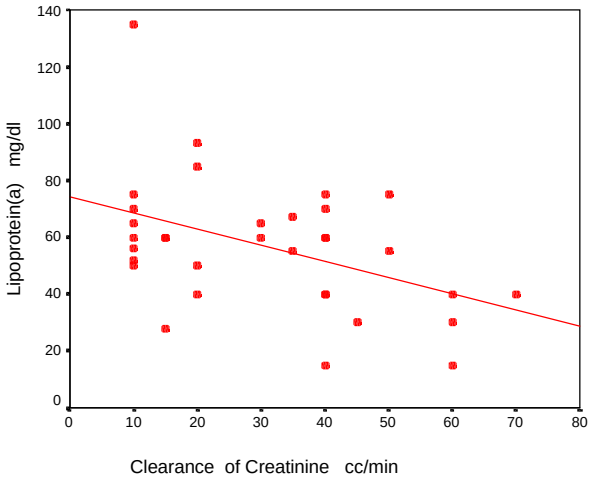

Figure 1. Significant linear inverse correlation of LP(a) with Clearance of Creatinine in CRF group(Group 2), [partial correlation test after adjustment for age (r = -0.441 p= 0.06)].

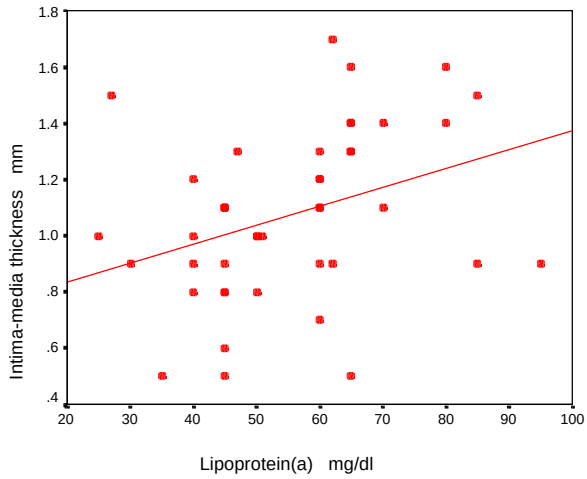

Figure 2. Significant positive correlation of carotid- IMT with serum LP(a) in hemodialysis patients (r =0.298 p= 0.029)

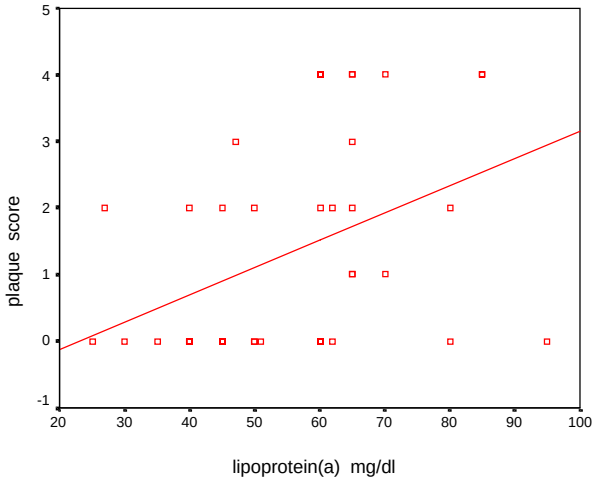

Figure 3. Significant positive correlation of plaque score with serum LP(a) in hemodialysis patients (r =0.375 p= 0.008).

Discussion

The principle findings of this study were firstly higher serum levels of lipoprotein (a), more thickening of carotid intima- media complex and more plaque occurrence of carotid-femoral artery in patients involved by chronic renal failure either predialysis or on hemodialysis, secondly positive correlation of serum LP(a) with carotid- IMT and plaque score only in hemodialysis patients. Pascasio et al. observed a large number of vascular plaques in uremia patients, he concluded that the process of advance atherosclerosis might be started with the beginning of renal failure, he suggested that hemo-dialysis treatment may not a potential factor to accelerate arthrosclerosis. Finally he concluded that the progression of atherosclerosis might be related to atherogenic factors operative before regular dialysis (18). Damjanovic et al. evaluated IMT of 45 dialysis patients found higher mean carotid IMT in HD patients than in control group. He showed positive correlation of IMT with certain risk factors for atherosclerosis (age, duration of dialysis and lipid parameters) (19). Correlation of IMT with ages and duration of hemodialysis in HD patients was evaluated, by Shoji and Hojs et al. no clear relationship of IMT with duration of hemodialysis treatment were found in their studies (20,21). Hojs also in his study (28 HD patients) observed, age was the only significant determinant of number of plaques, he concluded that hemodialysis patients had advanced atherosclerosis in the carotid arteries compared with normal subjects (21). More over Hojs in a recent study, showed no difference in plaque occurrence between 28 hemodialysis patients with 28 ESRD patients prior to hemodialysis (22). Savage et al. In a study on 24 dialysis patients noted on more prevalence of plaque in carotid and femoral artery, also this study showed the relationship between femoral artery plaque and ages of the subjects. Also he showed the correlation of age with IMT of carotid artery of HD patients (23). Moreover in a recent study by Kato et al. showed a significant correlation of IMT with age on 219 HD patients (12). Papagianni et al. in a study on 112 HD patients. showed a positive correlation of plaque score with age of the subjects (13). The present study showed positive relationship of LP(a) with IMT and also no clear relationship between LP(a) with IMT of CRF group was observed, while no differences between LP(a) and IMT of CRF and HD patients were found. Studies concerning the effect of LP(a) on IMT of normal persons showed various results. Sramek et al. on 142 asymptomatic men found no increased IMT in the carotid or femoral artery at high levels of Lp (a) he concluded that, Lp(a) levels are not associated with early atherosclerotic vessel wall changes in the carotid or femoral arteries (24). Dentil et al. in a study on 100 elderly subjects (aged 78.5±0.6), showed no association between carotid IMT and Lp (a), he concluded that the Lp (a) was unrelated to the severity of extra cranial vessels atherosclerosis (25) while Baldassarre et al. in a study on 100 type 2 hypercholestrolemic patients showed higher values of carotid IMT in hyrercholestrolemic patients with plasma Lp (a) levels > 30 mg/dl than in those with lower levels. He concluded that elevated plasma levels of Lp (a) can be considered an additional independent factor associated with thickening of carotid artery in patients with severe hyper-

cholesterolemia but not in those with moderate hypercholesterolemia or normocholestrolemic subjects (26). Finally Raitakari et al. on 241 healthy subjects suggested no association between IMT and Lp (a) but significant positive correlation with total Cholesterol, LDL-c, LDL/HDL ratio, age, and Tg were found (1). In renal failure patients the process of accelerated atherosclerosis is frequently seen. As the extraordinary high mortality in end-stage-renal disease (ESRD) patients under hemo-dialysis are due to cardiovascular disease ,there is some interest toward non traditional atherosclerotic cardiovascular disease risk factors that are Prevalent in ESRD Such as Lipoprotein(a) which needs to more attention because of its effect to acceleration of rapid progressive atherosclerosis seen in HD patients.

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